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Haploidentical Transplantation Using T Cell Replete Peripheral Blood Stem Cells and Myeloablative Conditioning in Patients with High-Risk Hematologic Malignancies Who Lack Conventional Donors is Well Tolerated and Produces Excellent Relapse-Free Survival: Results of a Prospective Phase II Trial

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Haploidentical hematopoietic stem cell transplant (HSCT) provides an opportunity for nearly all patients to benefit from HSCT. We conducted a trial of haploidentical T cell replete allografting using a busulfan-based myeloablative preparative regimen, peripheral blood stem cells (PBSCs) as the graft source, and posttransplantation cyclophosphamide (Cy). Eligibility was limited to patients at high risk of relapse after nonmyeloablative haploidentical bone marrow transplant (BMT). Twenty patients were enrolled in the study (11 with relapsed/refractory disease and 9 who underwent transplantation while in remission and considered standard risk). Donor engraftment occurred in all 20 patients with full donor T cell and myeloid chimerism by day +30. The cumulative incidence of grades II-IV and III-IV acute graft-versus-host disease (aGVHD) was 30% and 10%, respectively. The cumulative incidence of chronic GVHD (cGVHD) was 35%. Nonrelapse mortality (NRM) at 100 days and 1 year was 10% for all patients and 0% for standard-risk patients. With a median follow-up of 20 months, the estimated 1-year overall survival (OS) and disease-free survival (DFS) was 69% and 50%, respectively, for all patients, and 88% and 67% for standard-risk patients. Myeloablative haploidentical HSCT is associated with excellent rates of engraftment, GVHD, NRM, and DFS, and is a valid option in patients with high-risk malignancies who lack timely access to a conventional donor.

Biol Blood Marrow Transplant 18: 1859-1866 (2012)

KEY WORDS: Haploidentical, Myeloablative, Allogeneic, Peripheral blood stem cell

INTRODUCTION

Interest in haploidentical hematopoietic stem cell transplant (HSCT) originates from the immediate and almost universal availability of a one haplotype-mismatched family donor. This is a critical issue for the 70% of patients who do not have an available HLA-matched sibling donor and urgently need transplantation. A search for an HLA-matched volunteer unrelated donor (VUD) can identify a compatible donor for an additional 30% to 40% of patients. The chance of finding a suitable donor in the VUD registry significantly depends upon the racial and ethnic background of the transplantation recipient, ranging from 60% to 70% in whites, to about 10% to 20% for ethnic minorities. Furthermore, the successful application of VUD transplantation is hindered by the amount of time it takes from search initiation to allograft procurement. Many patients relapse or become ill while waiting for a VUD transplantation to begin. In contrast, a haploidentical family member can be identified and mobilized immediately in nearly all cases.

Until recently, haploidentical HSCT has been associated with disappointing clinical outcomes, limiting the widespread acceptance of this approach. Historically, T cell replete HSCT from haploidentical donors, using conventional posttransplantation immunosuppression, resulted in unacceptably high rates of

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Financial disclosure: See Acknowledgments on page 1865.

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Received April 22, 2012; accepted June 28, 2012

1083-8791/$36.00
http://dx.doi.org/10.1016/j.bbmt.2012.06.019

graft rejection, graft-versus-host disease (GVHD), and nonrelapse mortality (NRM) [1,2]. To address the risk of engraftment failure and GVHD, the Perugia Group pioneered a transplantation strategy based on antithymocyte globulin (ATG)-containing intensive conditioning, high peripheral blood stem cell (PBSC) content (median: 10^7 CD34+ cells/kg), and extensive ex vivo T cell depletion (median: 2×10^4 CD3+ cells/kg), which resulted in very low rates of graft rejection and GVHD [3]. However, as a result of the low T cell dose, the risk of serious infection and death from prolonged immune compromise in these patients remains high, with NRM estimated to be approximately 40%. Despite this, event-free survival rates for patients with high-risk acute leukemia is very promising, with 40% to 50% of patients who undergo transplantation while in remission surviving leukemia-free [4].

Investigators from Johns Hopkins University have pioneered an alternative approach to haploidentical HSCT strategy using a nonmyeloablative preparative regimen, followed by a T cell replete (unmanipulated) bone marrow (BM) graft. Posttransplantation high-dose cyclophosphamide (Cy) was administered on day +3 and +4 to control both GVHD and graft rejection in combination with tacrolimus and mycophenolate mofetil (MMF) [5]. This approach results in very low NRM (4% and 15% at 1 and 2 years, respectively) due to low rates of GVHD and infectious complications. Immune reconstitution was promising with low risk of cytomegalovirus (CMV) or invasive mold infections. Event-free survival at 1 and 2 years was 34% and 26%, respectively, with lymphoid malignancies responding significantly better than myeloid malignancies. Relapse was the major cause of treatment failure in this high-risk population of patients with poor-risk malignancies. Myeloablative conditioning and mobilized PBSC grafts have not been extensively studied in conjunction with T replete haploidentical transplantations using posttransplantation Cy.

In order to address the problem of relapse after nonmyeloablative T replete bone marrow transplant (BMT), we developed a phase II pilot study using myeloablative conditioning with a PBSC graft for T cell replete haploidentical transplantation. Intensification of the preparative regimen has been associated with a decreased risk of relapse after transplantation in high-risk malignancies, particularly myeloid malignancies [6]. In addition, the use of PBSC, rather than a BM graft, is associated with a higher incidence of chronic graft-versus-host disease (cGVHD) but decreased relapse rates, resulting in improvements in overall survival (OS) and disease-free survival (DFS) in patients with advanced stage hematologic malignancies [7].

Our study targeted younger patients, without a readily available matched related or unrelated donor (URD), who were perceived to be at a prohibitively high risk of relapse after a nonmyeloablative haploidentical BMT. The primary goal was to assess whether this approach would allow reliable engraftment with early donor T cell chimerism, and low rates of GVHD, infectious complications, and NRM. We also wanted to estimate the rate of relapse, event-free survival, and OS.

PATIENTS AND METHODS

Patients and Donors

Twenty patients were accrued to this protocol. Written informed consent was obtained for all of the patients in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board at Northside Hospital. Patients were eligible for inclusion if they were between 18 and 60 years of age, had a high-risk hematologic malignancy, were without a readily available matched related or URD, and had adequate organ function as defined by bilirubin <2, creatinine <2, cardiac ejection fraction ≥45%, pulmonary function ≥50% predicted, Karnofsky performance status ≥70%, and were human immunodeficiency virus negative. Donors were first-degree relatives (parent, child, or sibling) of the recipient and were matched at 3/6 to 5/6 loci (HLA-A, HLA-B, or HLA-DR) with the recipient. Donors were preferentially selected to minimize HLA mismatch in the host-versus-graft (HVG) direction. In addition, donors were selected to avoid a positive HLA crossmatch in the HVG direction or high-titer, donor-specific Abs as determined by the pretransplantation panel reactive Ab testing.

Conditioning Regimen and Postgrafting Immunosuppression

Initial transplantation conditioning consisted of fludarabine 30 mg/m^2/d on days −7 to −2, i.v. busulfan 130 mg/m^2/d on days −7 to −4, and Cy 14.5 mg/kg/d on days −3 and −2 in the first 5 patients. In response to increased rates of mucositis, fludarabine and busulfan doses were decreased by 30% and 15%, respectively, in the 15 subsequent patients (fludarabine 25 mg/m^2/d on days −6 to −2, i.v. busulfan 110 mg/m^2/d on days −7 to −4, and Cy 14.5 mg/kg/d on days −3 and −2). On day 0, patients received an unmanipulated PBSC allograft with a CD34 dose capped at 5×10^6/kg recipient weight. On days +3 and +4, patients received 2 doses of Cy 50 mg/kg/d with Mesna. Posttransplantation immunosuppression was initiated on day +5 with i.v. tacrolimus (target level 5-15 ng/mL) and oral MMF (15 mg/kg 3 times daily with a maximum daily dose of 3 gm). No immunosuppressive agents were administered until 24 hours after the last dose of posttransplantation Cy, including

corticosteroids. MMF and tacrolimus were discontinued without taper at days +35 and +180, respectively, in the absence of GVHD.

Supportive Care

Antimicrobial prophylaxis was administered according to institutional practice guidelines. Standard prophylaxis was started on day 0 including a quinolone antibiotic and acyclovir. Antifungal prophylaxis consisted of an echinocandin (caspofungin or micafungin) until day +5, when the patient was started on oral therapy with either voriconazole or posaconazole. Filgrastim 5 μg/kg was given daily starting on day +5 and continuing until neutrophil engraftment. Standard pneumocystis prophylaxis was started on day +30 and continued at least 6 months posttransplantation and until immunosuppression was discontinued. Quantitative CMV PCR was monitored weekly starting on day +1 and pre-emptive therapy initiated if viral reactivation was detected (≥400 copies/mL).

Chimerism Analysis

We assessed donor–recipient chimerism by the PCR-based amplification of a polymorphic short tandem repeat regions, followed by fragment separation by high resolution capillary electrophoresis (ABI 3130 XL Genetic Analyzer, Life Technologies, Grand Island, NY) and quantitation using GeneMapper Software (Life Technologies). Peripheral blood samples were collected for chimerism analysis on days 30, 60, and 90 after transplantation. Samples were separated into myeloid and T cell lymphoid fractions by indirect sorting with immunomagnetic beads (StemCell Technologies, Vancouver, British Columbia, Canada). Primary Abs were specific to CD33 and CD66b for myeloid cell and to CD3 for lymphoid T cell fractionation, respectively. The quality of sort was assessed using multiparametric flow cytometry (FACSCanto cytometer, DIVA analysis software; BD BioSciences, San Jose, CA). Genomic DNA was extracted from immunosorted cells and multiplex PCR was performed using commercial fluorescently labeled primer sets (ProfilerPlus, COfiler, NGM kits; Life Technologies). Four or 5-color fluorescence detection was performed on ABI 3130xl Genetic Analyzer and quantified using GeneMapper Software. For each informative short tandem repeat loci, allelic peak heights were determined, and the percentage of host alleles were calculated as [Σ(host alleles peak height)/(Σ(host + donor alleles peak heights)]*100. The range of the error of chimerism was determined to be nonuniform between different levels of chimerism and did not exceed 3.23%; 6.66%; 8.33%; 8.89%; 8.60%; 5.31%; and 3.07% for 1% to 5%; 6% to 20%; 21% to 40%; 41% to 60%; 61% to 80%; 81% to 95%; and 95% to 99% host, respectively. Ranges for chimerism error assessment were selected empirically in our laboratory.

Definitions and Study Endpoints

Neutrophil engraftment was defined as the first of 3 days of an absolute neutrophil count of $>0.5 \times 10^9$/L after transplantation. Platelet engraftment was defined as a platelet count of >20,000/μL without transfusion for the 7 preceding days. Acute GVHD (aGVHD) was scored based on the modified Keystone criteria [8]. Grades III-IV a GVHD were termed "severe" a GVHD. Chronic GVHD diagnosis and grading were based on the National Institutes of Health consensus criteria [9]. Patient outcomes are reported as of December 31, 2011. The major study endpoints were sustained donor engraftment, incidence and severity of GVHD, and NRM. Patients were considered to have died of NRM if there was no evidence of disease relapse or progression before death.

Statistical Methods

Probabilities of OS and DFS were estimated using the Kaplan-Meier product-limit method [10]. The cumulative incidents rates of NRM, relapse, aGVHD, and cGVHD were computed to take account of the presence of competing risks [11]. All survival outcomes were assessed between the relapsed/refractory group and the standard risk group at day 100 and 1 year, respectively, using the Wald test [11]. A survival outcome was determined to be significantly different between these 2 groups if the observed P value was <.05.

RESULTS

Patient and Graft Characteristics

A total of 20 patients with a median age of 44 years (range: 25-56 years) with high-risk hematologic malignancies were treated between January 2009 and March 2011. Patient characteristics are listed in Table 1. Eleven patients underwent transplantations with relapsed/refractory disease (acute myelogenous leukemia [AML]-5, chronic myelogenous leukemia-blast crisis [CML-BC]-1, acute lymphoblastic leukemia-2, non-Hodgkin lymphoma-1, Hodgkin's disease-1, chronic lymphocytic leukemia/Richters-1). Nine patients underwent transplantation with standard-risk disease (AML CR1 with poor-risk cytogenetics and/or induction failure, chronic myelogenous leukemia-chronic phase resistant to all tyrosine kinase inhibitors). Characteristics of the donors and allografts are listed in Table 2. The median (range) of HLA mismatch between donor and recipient was 5 (range: 2-5). Eighty percent of donor–recipient pairs were mismatched for at least 4 HLA loci.

Table 1. Patient Characteristics

	Patients (n = 20)	Disease	
Gender			
Male	9	Relapsed/refractory	11
Female	11	AML	5
		ALL	2
Age (years)		NHL (CLL-Richter [1 patient])	2
Median (range)	44 (25-56)	HD	1
		CML-BC	1
Preparative regimen			
Flu/Bu/Cy	20	Standard risk	9
		AML CR1 high risk	6
Stem cell source		Karyotype	
Peripheral blood	20	AML CR1 FLT3+	1
		CML-TKI resistant	2
HLA match			
5/10	14	HCT-CI	
6/10	2	0	9
7/10	3	1-2	9
8/10	1	3-5	2

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HD, Hodgkin's disease; CML-BC, chronic myelogenous leukemia-blast crisis; Flu, fludarabine; BU, busulfan; Cy, cyclophosphamide; TKI, tyrosine kinase inhibitor; HCT-CI, hematopoietic cell transplant comorbidity index.

Engraftment and Chimerism

Donor engraftment occurred in all 20 patients, with a median time to neutrophil and platelet recovery of 16 days (range: 14-21 days) and 27 days (range: 16-56 days), respectively. There were no late graft failures. Achievement of full donor chimerism was rapid with all evaluable patients achieving durable complete donor T cell and myeloid chimerism by day +30.

Regimen-Related Toxicity and Infectious Complications

Noninfectious fever (median Tmax 103.9; 101.2-106.8) developed in 18 of 20 patients within a median of 2.5 days (range: 1-5 days) transplantation and resolved in all patients after posttransplantation Cy administration (Figure 1). Excluding CMV reactivation, a total of 9 grade ≥III infections (severe, systemic infection requiring i.v. antibiotic or antifungal treatment, or hospitalization) occurred in 8 of 20 patients (40%) before day 30 (bacteremia: 5 patients; bacterial pneumonia: 1 patient; and viral pneumonia: 2 patients; Table 3). Two patients developed early fatal respiratory infections (*Burkholderia Cepacia*: 1 patient; and parainfluenza type 3: 1 patient). No invasive mold infections were detected. CMV reactivation (≥400 copies/mL) occurred in 13 of 16 at-risk patients (81%) and was treated pre-emptively, per institutional guidelines. CMV disease developed in only 1 patient (non-fatal enteritis on day +35 resolved promptly with treatment). One unexpected finding was a high rate of BK virus-associated cystitis, affecting 75% of patients and severe (requiring hospital admission for bladder irrigation and/or pain management) in 35%. The median posttransplantation day for developing cystitis was day 38 (range: 10-75 days).

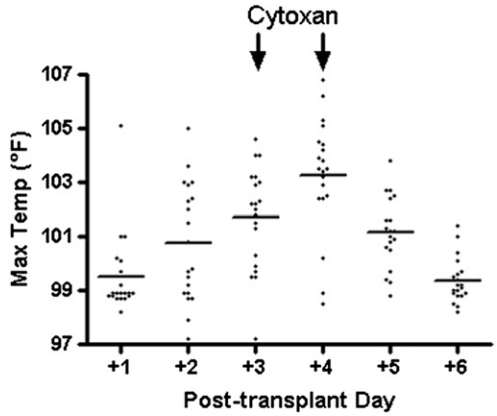

Figure 1. Posttransplantation fever curves. Points represent the Tmax of individual patients for the preceding 24 hours.

GVHD and NRM

The cumulative incidence of grades II-IV and grades III-IV aGVHD was 30% and 10%, respectively (Figure 2). Grades II-IV aGVHD was seen at a lower frequency in standard-risk patients compared with patients with relapsed/refractory disease (11% versus 46%; $P = .045$). With a median follow-up of

Table 2. Donor and Allograft Characteristics

Donors/Allografts (n = 20)		
Median donor age (range)	44	(20-70)
Donor–recipient relationship		
Parent–child	3	
Sibling–sibling	13	
Child–parent	4	
Donor–recipient gender matching		
Male → Male	6	
Male → Female	3	
Female → Male	5	
Female → Female	6	
Allograft characteristics		
Median CD34 dose (range) (x10e6/kg)	5.02	(4.03-5.08)
Median CD3 dose (range) (x10e7/kg)	17.35	(5.85-33.25)

Table 3. Grade ≥3 Infections to Day +30 Posttransplantation

Patients (n = 20)	
No. of patients with grade ≥3 infections	8
No. of grade ≥3 infections	9
Bacteremia	5
MRSE	3
Stenotrophomonas	2
Pneumonia	3
RSV	1
Parainfluenza, type 3	1
Burkholderia cepacia	1

MRSE indicates methicillin-resistant *Staphylococcus epidermidis;* RSV, respiratory syncytial virus.

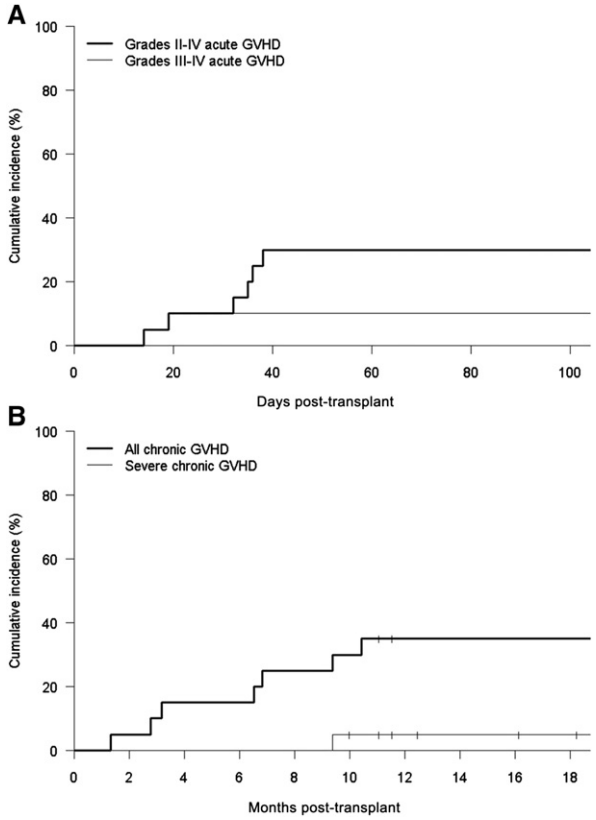

Figure 2. Cumulative incidence of (A) acute graft-versus-host disease (GVHD) and (B) chronic GVHD.

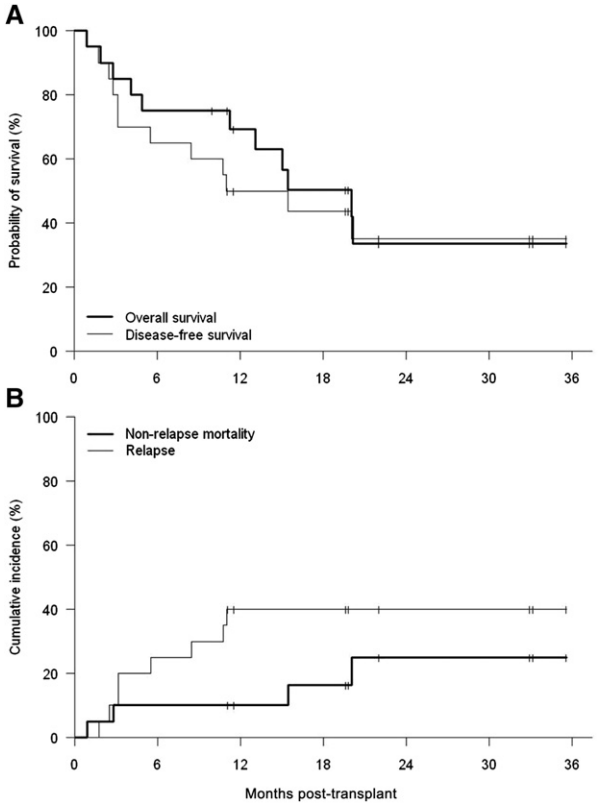

Figure 3. Probability of (A) overall and disease-free survival and (B) relapse and nonrelapse mortality.

20 months (range: 10-36 months) for surviving patients, the cumulative incidence of cGVHD was 35% and was severe in 5% of patients (Figure 2). There were no deaths attributable to aGVHD. One patient died approximately 20 months posttransplantation of bronchiolitis obliterans syndrome in the setting of cGVHD. NRM was 10% at 100 days and 1 year. For standard-risk patients, NRM was 0% at 100 days and 1 year.

Relapse, DFS, and OS

One-year estimates of OS, DFS, and relapse were 69%, 50%, and 40%, respectively, (Figure 3) for all patients, and 88%, 67%, and 33%, respectively, for standard-risk patients. After a median follow-up of 20 months, 9 patients remain alive and 8 of these remain disease-free. Causes of death are listed in Table 4.

DISCUSSION

In this report, we describe 20 adult patients with advanced hematologic malignancies who received myeloablative, T cell replete haploidentical PBSC transplants. Despite the presence of a median of 5 mismatches in the HVG direction, durable donor engraftment of T cells and hematopoietic cells was seen in all patients. The cumulative incidence rates of aGVHD and cGVHD were 30% and 35%, respectively, which are similar, if not slightly less, than expected with myeloablative PBSC transplants from HLA-matched donors. The 1-year NRM and OS 10% and 69%, respectively, for all patients, and 0% and 88%, respectively, for standard-risk patients. Remarkably, for a study of myeloablative transplantation from haploidentical donors, mortality from infection was low. Notably, serious CMV and invasive mold infections, which are principal causes of infectious death after allogeneic HSCT, accounted for no deaths in this study. BK virus–associated cystitis was a major cause of morbidity in these patients, but was nonfatal and resolved in all patients. The results of our study demonstrate that myeloablative T cell replete haploidentical HSCT is associated with promising rates of

Table 4. Causes of Death

	Patients (n = 20)
Relapse/progression	7
NRM	4
Respiratory failure	2
Parainfluenza pneumonia [1 patient]	
Bacterial pneumonia [1 patient]	
Septic shock	1
cGVHD/BOS	1

NRM indicates nonrelapse mortality; cGVHD, chronic graft-versus-host disease; BOS, bronchiolitis obliterans syndrome.

engraftment, GVHD, and NRM, making it a valid option in patients with high-risk malignancies who do not have HLA-matched donors.

In the past decade, there has been a growing interest in the use of haploidentical HSCT due to the rapid and nearly universal availability of donors, which is a critical issue in patients with advanced hematologic malignancies. Enthusiasm for this approach has been furthered by significant advances in the field and improvements in supportive care, which have allowed us to more safely provide transplantations for patients across HLA barriers while mitigating the historic issues of graft failure and GVHD. This study adds to a growing body of literature supporting haploidentical HSCT as a viable alternative for patients without rapidly available HLA-matched donors.

The optimal approach to performing haploidentical HSCT remains a matter of study. Aversa et al. [4] from Perugia have made major contributions to the field, showing that graft failure and GVHD can be reliably controlled using extensive ex vivo T cell depletion, an ATG-containing intensive conditioning regimen, and high CD34+ cell dose in the allograft, resulting in promising outcomes in patients with acute leukemia. Poor posttransplantation immunity and infectious mortality remain important barriers to the long-term success of this approach, and recent investigations have focused on improving immune reconstitution [12,13]. Furthermore, this approach requires complex and expensive cell selection techniques, which may not be universally available at all treating centers.

Huang et al. [14] at Peking University have avoided the requirement for ex vivo T cell depletion through the use of an ATG-containing intensive conditioning regimen and an augmented immunosuppression regimen containing cyclosporine, MMF, and methotrexate. Durable engraftment, low relapse rates and encouraging leukemia-free survival was noted, particularly in younger patients (<35 years of age). The incidence of grade II-IV aGVHD and cGVHD was much higher using this approach (55% and 74%, respectively). The high incidence of cGVHD may have contributed to both the low rates of disease recurrence as well as the increased NRM seen in older patients.

Another recent approach to myeloablative haploidentical allogeneic transplantation was recently described by Grosso et al. [15]. Donors underwent a nonmobilized apheresis on days −7 and −6 with cells infused into the recipient on day −5 after completion of total body irradiation (TBI) of 12 Gy. On days −3 and −2, patients received Cy 60 mg/kg/d × 2 days. On day 0, patients received an extensively T cell depleted PBSC allograft, along with posttransplantation immunosuppression. All but 2 of the 25 patients achieved durable engraftment. The incidence of grade II-IV aGVHD and NRM was 59% and 22%, respectively. Leukemia-free survival was encouraging in a high-risk patient population; however, our protocol seems to achieve at least similar outcomes without the need for ex vivo T cell depletion of the graft.

Luznik et al. [16] at Johns Hopkins University have taken a different approach based on the use of properly timed posttransplantation Cy to selectively target activated alloreactive T cells, which have been shown to be exquisitely sensitive to alkylator-induced cytotoxicity [17]. Studies in mice have established that posttransplantation Cy can inhibit both graft rejection and GVHD in mice receiving T cell replete transplants [16]. After a nonmyeloablative regimen of fludarabine, cyclophosphamide, and low-dose TBI of 200 cGy, patients receive an unmanipulated BM allograft, posttransplantation Cy, and conventional posttransplantation immunosuppression. Published results demonstrate low rates of GVHD and NRM, with promising survival outcomes particularly in patients with lymphoid malignancies [5]. Similar to other nonmyeloablative approaches, relapse remains the major source of treatment failure, particularly in patients with high-risk myeloid malignancies.

The current study tries to build on many of the successful strategies discussed previously. The use of posttransplantation Cy seems to provide adequate control of GVH-directed and HVG-directed alloreactive T cells to achieve reliable donor myeloid and T cell engraftment. In addition, unlike currently available ex vivo T cell depletion techniques, posttransplantation Cy seems to more selectively deplete activated alloreactive T cells, in contrast to resting T cells, which seems to result in better immune reconstitution [18]. Furthermore, there is no requirement for complex and costly cell section systems. Myeloablative conditioning and the use of PBSC as the cell source both likely contribute to better disease control in patients with high-risk hematologic malignancies. In this study, rates of aGVHD, cGVHD, and NRM compare favorably to myeloablative matched related and URD transplantations performed at our institution. Although overall efficacy is difficult to assess given the small numbers on the study and the poor disease risk of many patients, survival seems promising for patients with standard disease risk (majority of patients with AML who underwent transplantation while in remission), which is certainly comparable to that seen with HLA-matched donor HSCT.

Noninfectious fevers were experienced by virtually all patients between day 0 and day +5 after infusion of haploidentical T cell replete PBSCs. They may be related to cytokine release from proliferating alloreactive cells and consistent with this hypothesis, they usually resolve after administration of posttransplantation Cy. In our experience, these fevers seem to be both more frequent and more severe

(median Tmax 103.9°F) after this approach than seen after nonmyeloablative haploidentical BMT using posttransplantation Cy. These febrile episodes were managed with acetaminophen and cooling blankets, as it is our policy not to administer corticosteroids or other immunosuppressive agents before completion of the second dose of posttransplantation Cy. In murine models, properly timed Cy is based on the biological kinetics of T cell alloreactivity. Posttransplantation Cy is administered when alloreactive T cells are most susceptible to cytotoxicity. Corticosteroids, or any T cell immunosuppressive medication, will affect the kinetics of T cell activation and theoretically reduce the efficacy of posttransplantation Cy. It is possible that the selective nature of Cy-mediated T cell cytotoxicity results in improved immune recovery, compared with ex vivo T cell depletion. Consistent with this, a low rate of mortality from infections was seen in this study.

An unexpected finding of this study was the high incidence of hemorrhagic cystitis (HC). Although there was no mortality associated with this complication, it caused significant morbidity in patients (dysuria, urinary frequency), and 7 patients (35%) required hospital admission for bladder irrigation and/or i.v. analgesics. HC is a recognized complication of allogeneic transplantation therapy. Late-onset HC, occurring after engraftment, is due almost exclusively to reactivation of the polyoma BK virus. Other important risk factors associated with HC include busulfan-based conditioning, aGVHD, HLA-mismatched transplantations, and use of BM as the stem cell source [19-22]. Retrospective studies have shown high-dose busulfan, when combined with cyclophosphamide, to be a significant risk factor for the development of HC [19-22], particularly in the setting of HLA-mismatched transplantations, in which HC incidence ranges from 35% to 58% [19,23,24]. TBI, on the other hand, has been associated with significantly less risk of HC in both retrospective series (8% versus 32%) [25] and prospective randomized trials (10% versus 32%) [26]. In light of these findings, we have initiated a clinical trial of TBI-based myeloablative, T cell replete haploidentical HSCT.

The results of this approach to myeloablative haploidentical HSCT have been encouraging, and major historical barriers of graft rejection, GVHD, and NRM have been significantly addressed. Patients with advanced disease who are in remission at the time of transplantation seem to have excellent outcomes. However, results in patients who undergo transplantation with chemoresistant disease remain disappointing. The low rates of infectious complications and NRM suggest that this approach should be made available to better-risk patients earlier in the course of their disease.

ACKNOWLEDGMENTS

The authors are grateful to all of the clinicians and support staff at the Blood and Marrow Transplant Program at Northside Hospital for their excellent care of our patients who underwent transplantations.

Financial disclosure: The authors have nothing to disclose.

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